REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons which follow.

Claims 12-41 are requested to be canceled.

Claim 45 is currently amended.

Claims 47-62 are being added.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, are presented, with an appropriate defined status identifier. The cancellation of claim 12-41 is intended solely to cancel claims directed to non-elected inventions, and does not constitute an admission that any of the subject matter of the canceled claims is unpatentable. Applicant reserves the right to prosecute claims directed to the canceled subject matter in any appropriate application.

After amending the claims as set forth above, claims 1-11 and 42-57 are now pending in this application.

The claims currently under consideration concern fusion receptors, typically chimeric receptors, in which receptors that include domains of one or more of mGluR, CaR, and $GABA_B$ receptors are fused with a G-protein. Such fusion receptors thus allow signal tranduction switching. For example, most of the mGluR types couple with a G-protein that affects adenylate cyclase. Detection of cellular changes resulting from this linkage is not amenable to high throughput screening. Thus, for example, if the intracellular domain of a CaR is used, it can be fused to a G-protein that activates phospholipase C, allowing high throughput screening based on intracellular calcium levels, which was not possible if the G-protein normally interacting with the mGluR affecting adenylate cyclase was used in the fusion.

As indicated above, new claims 47-62 are submitted. Claim 47 specifies at least 75% sequence identity; support for this is provided for example at p.3, line 15. Claims 48-53 specify particular mGluR types; support for these types is provided for example at p.4, lines 20-28. Claim 54 specifies $GABA_B$ receptor domains; support is provided for example in original claim 1. Claims 55 and 56 specify chimeric G protein; support is provided for example at p.13, line 20.

Claims 57-62 specify at least 90% sequence identity. Claim 57 specifies that the extracellular domain sequence is from mGluR, and the transmembrane domain is from mGluR or CaR, and the extracellular domain sequence is from CaR. Claim 60 specifies that the extracellular domain sequence is from $GABA_B$ receptor, the transmembrane domain sequence is from $GABA_B$ receptor or CaR, and the intracellular domain sequence from CaR. Support for these claims is provided for example at p.3, line 15 and in original claim 1. Claims 57-62 thus concern particular constructs that include either mGluR or $GABA_B$ receptor extracellular domain, and a CaR intracellular domain.

Thus, no new matter is presented in the new claims.

Rejections under 35 U.S.C. 112 paragraph 1

The Examiner rejected claims 1-11 and 42-46 under 35 U.S.C. 112 first paragraph, asserting that the scope of the claim is not enabled. The Examiner asserted that undue experimentation would be required to practice the invention. Applicant respectfully traverses these rejections.

The Examiner's rejections appear to rest on the basis that the specification does not provide sufficient guidance for one of ordinary skill in the art to produce fusion receptors that have variations in the sequences in the extracellular, transmembrane, and intracellular domains from the natural domain sequences without undue experimentation. Contrary to the Examiner's assertion, substantial guidance is provided, so that, in combination with the knowledge of one of ordinary skill in the art, the claimed fusion receptors can be produced without undue

experimentation. In particular it should be understood that one of ordinary skill in the art recognizes that many residues in active proteins can be altered without destroying activity, and a variety of standard molecular biology techniques are available to produce nucleic acid sequences encoding such modified proteins.

In addition, Applicant has provided information on how to determine where modifications can be made to the respective receptor domains in the present invention. Thus, in addition to the specific fusion receptor constructs described in the specification, Applicant has also described how to conveniently identify residues that likely can be altered or deleted without destroying activity. At pages 16-17, Applicant describes how to use alignment of different receptors and of receptors from different sources for identification of conserved and variable residues to identify portions of the receptor sequences that can likely be varied without destroying activity. Further, Applicant points out the well-known conservative substitutions of similar amino acid residues, and on page 18 indicates that the encoding nucleic acid sequences can utilize degenerate condons. Thus, Applicant has provided guidance so that one of ordinary skill in the art can produce many sequence variants without undue experimentation.

In contrast to the guidance provided by Applicant, in making the rejections the Examiner has not shown how undue experimentation would be required to practice the invention. Given the guidance pointed out above, one of ordinary skill in the art could identify portions of a domain sequence susceptible to modification, make modifications in such portion or portions, and test the resulting receptors for activity. None of that process would involve undue experimentation. Thus, Applicant respectfully submits that the present claimed invention is enabled, and requests that the Examiner reconsider and withdraw the rejections.

Rejection under 35 U.S.C. § 112, paragraph 2

The Examiner rejected claim 45 under 35 U.S.C. § 112, second paragraph as allegedly being indefinite due to the reference to "mRIuR". Claim 45 is amended above to correct the typographical error such that the claim now refers to "mGluR". Applicant respectfully submits that this amendment obviates the Examiner's rejection.

Rejection under 35 U.S.C. § 103

The Examiner rejected claims 1-11 and 42-46 under 35 U.S.C. § 103 as allegedly being obvious over Fuller et al. in view of Bertin et al., further in view of Negalescu et al., further in view of Kaupmann et al., and further in view of Rock et al. The Examiner asserted that one of ordinary skill in the art would have been motivated to produce a G-protein fusion protein comprising a promiscuous G-protein in order to produce the best chance of identifying functional fusion proteins. Applicant respectfully traverses these rejections.

Applicant respectfully submits that the Examiner is improperly using hindsight to combine references to lead to the present invention. In addition, even though the Examiner asserts that a particular motivation to produce the claimed fusion receptors exists, no evidence showing that such a motivation would, in fact, have existed. To the contrary, Applicant respectfully submits that the Examiner's assertion of the motivation also involves improper use of hindsight.

In order to combine references in establishing a prima facie case of obviousness, the Federal Circuit has consistently held that there must be a suggestion or motivation from the art to make such a combination. For example, in *In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999), the court indicated that "Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references." Further, in *In re Kotzab*, 54 USPQ2d 1308, 1316 (Fed. Cir. 2000) the court stated that in order "to establish obviousness based on a combination of the elements disclosed in the prior art, there

must be some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant."

In the present case, the Examiner has combined five different references, and states that the motivation to produce the present fusion receptors is seen when the references are taken together. This assertion just conflates the required analysis. As indicated, there must be a suggestion or motivation to combine the references in the first place. Only if there is such a suggestion to combine the references does the analysis proceed to determine whether the combination of references leads to the claimed invention. The mere presence of elements in each of the references that might be related to the present invention does not provide either the suggestion to combine the references, nor does it show that combining the references leads to the claimed invention to make the invention obvious.

While the Examiner has cited the five different references and asserted that specific portions of the descriptions in those references can be combined in a manner leading to the present invention, the Examiner does not appear to have performed a proper analysis. A proper analysis, as directed by the Federal Circuit, involves considering whether there is a suggestion or motivation from the prior art to combine the cited references. In considering whether such suggestion exists, the entire disclosures of the references must be considered, i.e., it is improper to pick and choose portions of the disclosures while ignoring portions that would direct one of ordinary skill in the art away from the claimed invention.

Thus, briefly considering each reference, Fuller et al. describes chimeric receptors that include domains of mGluR and/or CaR, but does not describe fusion of such chimeric receptors.

As previously discussed, Bertin et al. describes fusion of a specific type of receptor, an adrenoreceptor, to G-protein alpha subunit with which the adrenoreceptor normally associates. The stated purpose of the Bertin fusion was to isolate the G-protein interaction to the single G-protein as a method of analyzing the pathways activated by the receptor through G-proteins, e.g., because the adrenoreceptor may couple with multiple different G alphas thereby activating

multiple pathways. There is no suggestion of using mGluR, CaR, and/or $GABA_B$ receptor domains (e.g., as in present claims 57-62); in particular there is no suggestion to create fusion receptors using mGluR, CaR, and/or $GABA_B$ receptor domains. Further, nothing in this reference suggests signal transduction switching or any other use of a non-natural G-protein as specified in claim 1. To the contrary, the entire focus is on analyzing normal adrenoreceptor-linked pathways, utilizing normally interacting adrenoreceptors and G alphas. In fact, utilizing a non-natural G-protein would be directly contrary to the entire purpose of the Bertin work, as it would not then be useful to elucidate the pathways which the receptor normally activates.

Also as previously discussed, Negalescu et al. describes the promiscuous $G\alpha_{15}$ and $G\alpha_{16}$. Negalescu et al. also describes the use of such promiscuous $G\alpha$ interacting with intact G-protein coupled receptors (not chimeric receptors). There is no suggestion that the $G\alpha_{15}$ or $G\alpha_{16}$ should be fused to the receptor. To the contrary, Negalescu et al. indicates that typically the G-protein coupled receptor will not even be under the control of the control sequence controlling promiscuous $G\alpha$ expression. Thus, not only is the receptor not fused with the $G\alpha$, expression is not even co-regulated. Thus, the reference is directed to use of separately expressed $G\alpha$ and receptor. In effect, such separate expression teaches away from the presently claimed fusion receptors, instead teaching use of non-covalent interaction. Therefore, even if we assume for the sake of discussion that there were a suggestion to combine this reference with Fuller et al. (which is not admitted), the combination would not lead to the present invention, instead it would be directed to separate expression of chimeric receptor and G-protein.

Kaupmann et al. describes purified $GABA_B$ receptors from rat and human, and the use of such receptors in screening for modulators. Applicant finds no suggestion from Kaupmann for creation of $GABA_B$ receptors fused with G-proteins, and specifically not with G-proteins with which the receptor does not normally interact, and no suggestion for creation of chimeric receptors.

Finally, Rock et al. describes a fusion protein that includes human chorionic gonadotropin (hCG) linked via a nine amino acid linker to enterotoxin subunit B, and the use of the fusion protein to induce hCG-specific antibodies without additional adjuvents. There is no description or suggestion that such linkers of any type, including peptide linkers should or even could be used to functionally link a CaR, mGluR, or $GABA_B$ receptor intracellular domain with a non-natural G-protein subunit. The sole focus of Rock et al. is on induction of antibody production. The Examiner has provided no evidence that the use a linker to effectively create a more immunogenic hCG suggests anything about the use of linkers between the receptors described in the present claims and a G-protein. Thus, Applicant does not see how any suggestion can be present to combine this reference with Fuller et al. and/or with any of the other cited references.

As a minimum, the Examiner's obviousness rejection would require that there by a suggestion to combine Fuller et al., Bertin et al., and Negalescu et al. In accordance with the brief summary of the cited references, no suggestion or motivation is apparent to combine these cited references in any way to lead to the present invention. In particular, Applicant submits that there is no suggestion to combine a reference that is focused on elucidating natural pathways using a specific receptor fused with its natural Gα (Bertin et al.), with a reference that teaches using separately regulated promiscuous Gα proteins, i.e., Gα proteins that will associate in the cell with a number of different receptor intracellular domains (Negalescu et al.). In fact, using the promiscuous Gα proteins described in Negalescu et al. in the fusion of Bertin et al. would be directly contrary to the purpose for making the Bertin fusion, i.e., elucidating natural pathways. Thus, the only motivation to combine these references appears to come from the present disclosure. Consequently, combining these references in relation to the present invention involves improper use of hindsight to select only portions of references to re-create the present invention.

Likewise, there is no suggestion to combine Fuller et al. with Bertin et al. Once again, Bertin et al. is focused on elucidating natural pathways by using a fusion between an adrenoreceptor and a natural Gα in order to eliminate interactions with different Gα proteins that

can activate other pathways. Fuller et al. is not directed to such pathway analysis, instead describing the use of chimeric receptors for identifying compounds that act on specific domains of mGluR and/or CaR. Thus, there is no reason apparent why a person of ordinary skill in the art would combine these references.

In view of the lack of suggestion or motivation to combine the cited references, Applicant respectfully submits that the Examiner has failed to properly make a prima facie case of obviousness.

In addition, as indicated above, the Examiner asserted that one of ordinary skill in the art would have been motivated to produce a G-protein fusion protein comprising a promiscuous G-protein in order to produce the best chance of identifying functional fusion proteins. However, the Examiner does not provide any evidence supporting this asserted motivation. In addition, even if we assume for the sake of argument that the Examiner is correct that one of ordinary skill in the art would be motivated to create a fusion between a G-protein and an intracellular domain of a mGluR, CaR, or GABA B receptor, the Examiner has failed to provide any evidence that such a person would choose to utilize a G-protein that does not normally associate with that receptor domain instead of the naturally associating G-protein as was done in Bertin. Thus, even if the Examiner's assumption is correct (an assumption for which the Examiner did not provide support and with which Applicant does not agree), it would lead to a construct more similar to that described in Bertin rather than the present claimed fusion receptors of claim 1.

Further, contrary to what is required in making an obviousness rejection, the Examiner has not shown why one of ordinary skill in the art, with no knowledge of the present invention, would have selected only portions of the disclosures from the cited references to produce the present invention. In picking and choosing portions from each of a number of references, the Examiner again has not considered the matter properly, as a proper obviousness analysis cannot be performed with this type of selection. Instead, each of the references must be considered as a whole for what they teach to one of ordinary skill in the art. As discussed above, when Bertin and Negalescu are considered in their entireties, it is apparent that there is no suggestion to select

only (1) fusion of Galpha with receptor (Bertin) and (2) promiscuous Galphas. Without such a suggestion to select only those limited portions of the descriptions, there is no suggestion or motivation to combine these references in any way that might lead to the present invention.

Therefore, Applicant respectfully submits that there simply is no suggestion or motivation from the cited art to select the specific elements from the various pieces of cited art and combine them in an attempt to lead to the present invention.

Applicant respectfully submits that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872. If any additional extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

Date 14 August 2003

By _____

FOLEY & LARDNER
P.O. Box 80278
San Diego, California 92138-0278
Telephone: (858) 847-6714
Facsimile: (858) 792-6773

Wesley B. Ames
Attorney for Applicant
Registration No. 40,893